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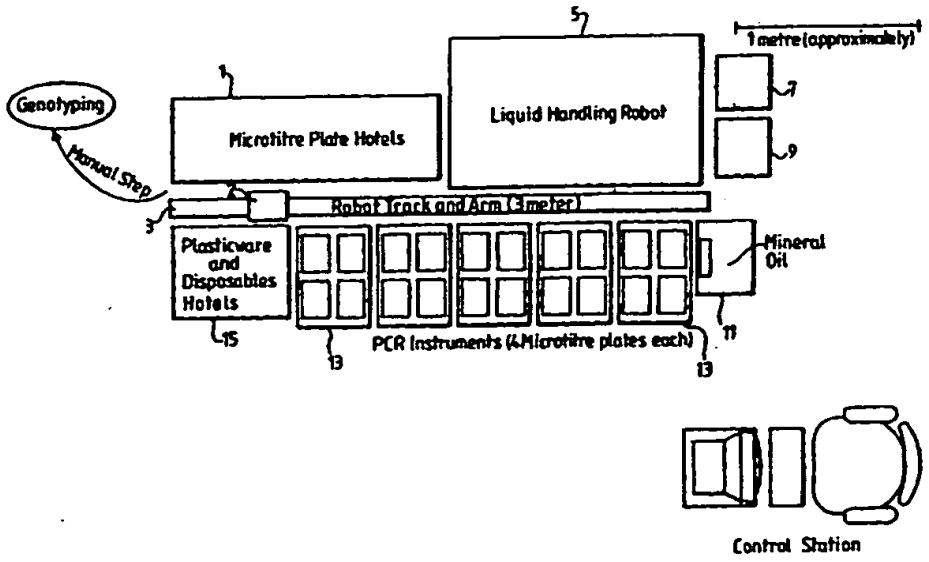

(57) Abstract

The present invention relates to an apparatus and method for processing biochemical samples, and in particular an apparatus for discharging pipettes from a dispensing device and a method of dispensing aliquots of viscous liquid during a biochemical processing operation. A sample processing apparatus according to the invention has a number of processing mechanisms, each adapted for processing one or more microtitre plates. A robot arm (2) is configured for translation of motion along a track (3) to access processing mechanisms on either side of the track. The arm has several degrees of freedom and the fingers of the robot arm are selected to allow the reliable handling of microtitre plates. Preferably, the transportation and the processing mechanisms are controlled by a common control system so that coordinated motion is achieved.

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SAMPLE PROCESSING APPARATUS AND METHOD

FIELD OF THE INVENTION

The present invention relates to apparatuses and methods for processing chemical or biochemical samples.

BACKGROUND

Progress in biotechnology presently requires the processing of a large number of biochemical samples. Genotyping, that is to say the mapping of chromosomes on DNA, requires investigation of an enormous number of samples, since from each sample is obtained only a small amount of information while the total information encoded by the chromosomes is immense.

Such processing is of course highly labour intensive, and so far only limited progress has been made in automating the operation. Furthermore such progress as there is has been limited to automation of a single processing step.

For example, one known dispensing device is adapted to perform the step of inserting aliquots of liquid material into respective depressions (hereinafter "wells") formed in a rectangular array on a major surface of a plate. Each well on the plate (known as a "microtitre plate") acts as a reaction vessel. The dispensing device has a pipetting head including a plurality of pipetting elements arranged in a row, each of which elements is designed to hold a downwardly projecting disposable tip. The head is moved automatically to a position over a rack of disposable

tips, so that each pipetting element is above a respective tip, then the head is lowered and each pipetting element picks up a tip. The head then moves to insert the tips in sequence into reservoirs of reagent fluid, from which an aliquot of fluid is taken up into each tip. The tips are then inserted into respective wells in a row on a microtitre plate, where the fluid is dispensed. If desired, further liquid samples are placed into the wells using the same respective tips. The dispensing device then discards the tips, by releasing them from a height into a container, and a second batch of tips is taken up for dispensing material into a second row of wells.

During the process the microtitre plate is static, but it must afterwards be moved along a sequence of further processing devices, for example into a reaction chamber which is cycled at the correct temperatures to enable a chemical reaction to proceed under the control of a program stored in a database.

THE INVENTION

The general aim herein is to provide new and useful apparatus and methods for processing biochemical or chemical samples.

A preferred object of the present invention is to increase the capacity and reproducibility of the processing of biochemical samples.

In its most general terms, the present invention seeks to facilitate automatic processing of biochemical

samples. It thus presents a novel production line approach to biotechnical processing.

Accordingly, in a first aspect, the invention proposes a sample processing apparatus comprising a plurality of processing stations, each adapted for processing one or more microtitre plates, and transportation mechanism for transporting microtitre plates sequentially between the processing stations, whereby the one or more microtitre plates are sequentially processed.

Preferably, the transportation mechanism includes at least one artificial arm, that is to say a device having several degrees of freedom of movement and including a gripping portion ("hand") at a free end of a movable shaft ("arm").

Preferably the transportation mechanism and the processing stations are controlled by a common control system, so that coordinated motion is achieved. For example, upon transportation of a microtitre plate to a given processing mechanism, the control system is preferably capable of transmitting an initiation signal to that processing mechanism to initiate processing.

The control system is preferably adapted so that while a given first processing mechanism is processing a first plate, the transportation means is employed in transporting a second plate to a second processing device, so that the transportation means is used efficiently.

In a second aspect, the invention provides a sample processing apparatus comprising at least one processing mechanism for processing one or more microtitre plates, the apparatus including an error detection means for detecting an error made in the processing of the plate or plates, and means for adopting an appropriate error correction strategy. The method of detecting an error in a sample processing apparatus and adopting an appropriate error strategy constitutes a third aspect of the invention.

For example, if the processing mechanism is the known dispensing device described above, the error detection means may detect that a pipette tip has been incorrectly taken up, so that a replacement pipette tip can be provided.

Additionally or alternatively, the error detection means may be able to alert the operator of the system to processing faults, for example by E-mail or by illumination of a display device. For example, if the dispensing apparatus runs out of disposable tips, the operator may be informed of the shortfall, so that further stocks may be procured. Signals may additionally be sent to other elements of the processing apparatus, for example to a transportation device, so that they react accordingly, ceasing to process plates or processing plates in an alternative order.

In a fourth aspect the invention provides a method for dispensing a viscous fluid, such as oil, into a

plurality of wells formed in a rectangular array on the upper surface of a microtitre plate, the method comprising translating the plate parallel to a first axis of the rectangular array, inserting a plurality of downwardly projecting filaments spaced apart parallel to the other axis of the rectangular array successively into respective wells, and dispensing said fluid via said filaments.

Preferably, the filaments are well fillers such as "Q-fill" or "PBA well filler", having a hollow body into which the oil is pumped and a plurality of capillary tubes extending from the hollow body through which the oil can pass. The capillary tubes are aligned with their respective wells and the oil dispensed into the wells in drops.

This manner of dispensing oil is simpler than by the employment of a pipetting device as described above, while nevertheless ensuring that oil is dispensed in a uniform manner, and without leakage problems due to the viscosity of the oil.

There may be further provided a discharge apparatus for discharging used pipette tips from a dispensing device, such as the known dispensing device described above. The device includes one or more elements for holding pipette tips, and means for bringing the one or more holding elements into contact with tips and then downwardly displacing the one or more elements so as to remove the tips from the pipetting device.

Thus, pipette tips may be discharged in a regular manner, which permits them to be re-cycled automatically.

Embodiments of the present invention will now be described with reference to the accompanying drawings in which:

Figure 1 shows a schematic top view of a sample processing apparatus according to the invention; and

Figure 2, shows an apparatus according to the invention for removing pipette tips, (a) in perspective view, (b) in front view and (c) in side view.

The apparatus includes a microtitre plate hotel 1, a rack which houses a large number of microtitre plates. The plates are held with their upper surface, that is to say the surface defining the wells, horizontally uppermost. The hotel 1 stores the plates in an upright rectangular array. Normally plates holding 96 or 384 wells are employed.

A robot arm 2 is configured for translational motion along a 3 metre track 3, to access processing mechanisms on either side of the track. The arm has 6 degrees of freedom, namely linear translation along the rail, rotation at its shoulder, elbow, and wrist, twist and grip. The fingers of the robot arm are selected to allow the reliable handling of microtitre plates. In other embodiments the length of the track will be different (eg. 1m or 9m) depending upon the number of processing mechanisms and their arrangement.

Initially, the robot arm 2 successively moves a

number of microtitre plates (eg. 10 or 15) from the plate hotel 1 to the liquid handling robot 5. This liquid handling robot is a prior art dispensing device of the kind described above. It includes eight independent, variably spaced pipetting elements, one for each well of a row of wells on the microtitre plate. The pipetting elements are each xyz programmable and capable of taking up a respective disposable pipette tip from a rack of unused tips 7. The robot 5 dispenses an aliquot of a number of DNA samples into respective wells on each plate (ie. a predetermined amount of a first DNA sample into a first well on a first plate, and into a first well on a second plate, etc.). A different disposable pipette tip is used for each DNA sample. These tips are then discarded, or recycled. The robot then dispenses, using a further tip; an aliquot of a first reactant into each well of a first microtitre plate. Continuing the process, a number of reagents are aliquotted using respective pipette tips into every well of the respective plates. The number of reagents thus equals the number of plates used, while the number of DNA samples equals the number of wells on each plate. Each combination of reagents and sample is realised in one well. The total number of pipettes used equals the number of DNA samples plus the number of reagents.

The disposable tips are then removed from the liquid handling robot 5 by a discharge apparatus 9. The discharge apparatus includes a number of racks for

pipette tips. It first raises a rack so that each tip held by the robot 5 enters the rack, then the robot 5 releases the tips, and then the rack is displaced downwardly. The discharge apparatus 9 thus arranges the disposable tips for recycling.

The recycling of tips may reduce by more than 50% the number of disposable tips required for the liquid handling manipulations. Preferably, the tips are not washed or sterilised; rather the approach is to schedule their reuse at appropriate points in the sample processing. For example, a pipette may be reused to perform an operation on a well which it has already treated. Whilst it is possible to duplicate this recycling manually, the risk of error makes this form of recycling undesirable in other than an automatic process.

When all wells of a first plate have been thus treated (and while the liquid handling robot 5 is still filling the other plates), the robot arm moves the first microtitre plate to the mineral oil dispensing device 11, which implements the dispensing method according to the invention.

The oil dispensing device 11 has means for translating the microtitre plate in its plane parallel to one of the axes of the rectangular array of wells. A plurality of filaments project downwardly toward respective wells, and as the wells pass underneath inject an aliquot of oil. Thus, oil can be inserted in a uniform way into the wells.

From the oil dispensing device, the robot arm 2 carries the plate to a free location on one of five Peltier thermal cycling engines, each designed to perform PCR (Polymerase chain reaction) on up to four microtitre plates containing DNA and reactants. The control system monitors the PCR machines 13 to ensure that the robot 2 places each plate into a vacant position in a PCR.

The products of the PCR can then be pooled. This pooling may be performed by the liquid handling robot 5 to which are supplied, say, seven processed plates and a single empty plate. The liquid handling robot removes an aliquot of liquid from beneath the oil layer of corresponding wells on the processed plates and pools these samples in a well on the empty plate. Thus, each well of the (formerly) empty plate receives a respective DNA sample, different portions of which have been treated with different reagents. The number of plates pooled in this way depends upon the biochemical operation which the complete system is performing, and the role of those plates within it.

The pooled plate may then be used for preparing gels for analysis. The loading of gels may be manual, as shown, or, more preferably, using a further automatic processing mechanism (not shown), of which the operation may, for example, be integrated with the rest of the system and coordinated by the main control computer.

The system further includes a control computer connected to other elements of the system by leads (not

shown). The control computer runs custom programs written eg. in Visual Basic with automatic links to further software running in the background. The control system also includes means for sensing errors, with means for taking corrective action and/or informing an operator. For example, the system itself might sense that a rack of fresh pipette tips is exhausted and use the robot arm to place the exhausted rack by a full one. Alternatively or additionally, the system may be capable of detecting that a given PCR machine 13 is not functioning and diverting work to other PCR machines. Optionally, when the system itself corrects an error, a human operator may be informed, at once or subsequently.

Certain errors, however, such as the complete exhaustion of reserves of material, require corrective action by the operator. For some, the operator must take action at once, while others do not require immediate attention. In either case, the control system alerts the operator, for example by E-MAIL, that the error has occurred.

Turning to Figure 2, a device 9 is shown for discharging pipette tips from the liquid handling robot 5. Each of the brackets 15 is for holding a rack for pipette tips. Each rack contains a plurality of upwardly directed holes for receiving respective downwardly directed tips. The brackets 15 are moved vertically using a motor 17 with a bevel gear arrangement 19. Other embodiments are possible in which the rack is moved using

one or more electric pneumatic pistons.

When it is desired to remove the tips from the liquid handling robot 5, the racks are aligned with their holes beneath respective tips. The rack is then moved vertically so that the tips are inserted into the holes. The tips are thus supported when they are released by the liquid handling robot, and the racks can then be lowered, holding the tips. The vertical movement of racks permits a dense filling of the racks, while ensuring that the tips do not have far to fall, and can hence be removed for recycling in a consistent, and thus manageable, manner.

Disposable tips capable of liquid detection may be used by the liquid handling robot. These include carbon-conductive coated pipette tips which when an ionic solution is present send a conductive signal. This signal is preferably detected by a processing mechanism such as a known dispensing device. The liquid detection tips are held for example, in units of 96 tips in an 8 by 12 array. The liquid handling robot takes 8 tips at a time and uses them to aliquot liquids. The disposable tips are normally ejected to waste.

When using the discharge apparatus 9 as a tip recycler, the systems looks ahead at samples due to be processed and determines whether the same liquid is to be aliquoted again. If this is the case, and the operator has selected the tip recycling option, the used tips are returned to their original location in the tip rack

rather than being ejected to waste.

The liquid handling robot 5 ejects disposable tips by moving to the top of the robot 5 thereby pushing the tips off. In order to ensure that the used tips return reliably to their original location in the tip rack, the liquid handling robot moves to the correct location, the tip recycler raises the tip rack to the top of the liquid handling robot which then ejects the tips in the normal manner. The tips fall into their original location and the tip recycler lowers the tip rack again. The liquid handling robot 5 moves to the next location and picks up another 8 tips.

This repeats until this part of the process is complete. The system then uses the disposable tips which have been returned to the tip rack when appropriate, ie, when it is aliquoting the same liquid again. The systems ensures that the tips are not used to aliquot different liquids thereby avoiding contamination. Once the system determines that the tips have been used for the last time then the tips are ejected to waste. An option exists to return the tips on all occasions thereby allowing the operator to recover the tip rack and use it again in another process which uses the same liquids, although this is not recommended.

If the apparatus is to accommodate microtitre plates have 384 wells in a 24 by 16 array, the volumes of fluid used may be such that there is no room left in the wells for the oil. In such a situation, the apparatus may

provide a further processing mechanism for sealing the wells by, for example heat, pressing a plastic layer over the top of the wells. This will then provide the same effect as the oil, namely to prevent the reaction fluid evaporating. The technique of using plastic seals of course, may be used on plates having 96 wells.

To remove the liquid from the wells the plastic seal has to be pierced or broken in some way. This could be achieved by using the tips on the liquid handling robot to pierce the plastic or by providing a separate unit hence a plurality (in this case 384 or 96) spikes which can pierce the respective seals or by providing a further heating element which melts the plastic seal such that it breaks open.

An example of any automated genotyping production line can be seen in Table 1. This shows a simplified flow diagram for single microtitre plate of DNA, not exceeding liquid handling robot or thermal cycling unit capacities.

Although the invention has been described above in relation to a single embodiment, many variations are possible within the scope of the invention as will be clear to a skilled person.

TABLE 1

Simplified flow diagram for single microtitre plate of DNA, not exceeding Liquid Handling Robot or Thermal Cycling Unit capacities

From	To		Action	By
Micro-titre Plate Hotel	Liquid Handling Robot	1	Move microtitre plate containing DNA	Robot Arm
Micro-titre Plate Hotel	Liquid Handling Robot	2	Move empty microtitre plate for PCR product	Robot Arm
		3	*Repeat from step 2 until at Liquid Handling Robot capacity or all required microtitre plates loaded*	
		4	Aliquot DNA from DNA microtitre plate to empty microtitre plate(s)	Liquid Hand-ling Robot
		5	Aliquot reagents to microtitre plate containing aliquoted DNA	Liquid Hand-ling Robot
Liquid Handling Robot	Mineral Oil Dispenser	6	Move microtitre plate containing DNA and reagents	Robot Arm
		7	Add mineral oil to cover PCR reaction mixture	Mineral Oil Dis-penser Robot
Mineral Oil Dispenser	Thermal Cycling Unit	8	Move microtitre plate containing DNA, reagents and mineral oil	Arm
		9	Start thermal cycling procedure	Thermal Cycling Unit
		10	*Repeat from step 5 until at PCR Thermal Cycling capacity or all required microtitre plates removed*	
Micro-titre Plate Hotel	Liquid Handling Robot	11	Move empty microtitre plate for Pooling	Robot Arm Robot Arm

Thermal Cycling Unit	Liquid Handling Robot	12	Move microtitre plate containing PCR product	Robot Arm
		13	*Repeat from step 11 until all microtitre plates containing PCR product required for this pool moved*	
		14	Aliquot PCR product from under mineral oil to pool plate, combining PCR products	Liquid Hand-ling Robot
Liquid Handling Robot	Micro-titre Plate Hotel	15	Move pool microtitre plate containing pooled PCR products	Robot Arm
Liquid Handling Robot	Micro-titre Plate Hotel	16	Move microtitre plate containing PCR product	Robot Arm
		17	*Repeat from step 16 until all microtitre plates containing PCR product moved*	
		18	*Repeat from step 11 until all microtitre plates containing PCR product required for next pool moved.*	
		19	*Repeat from step 18 until all pooling completed*	

Note: In normal use the process flow would be more complex, for example, additional DNA aliquoting, addition of reagents being done whilst thermal cycling was underway.

CLAIMS

1. Sample processing apparatus for processing chemical and biochemical samples, comprising

a plurality of processing stations, each processing station being adapted to receive microtire plate and comprising processing means for carrying out a respective process in relation to the microtitre plate;

transportation mechanism to transport microtitre plates between the processing stations, and

a control system for controlling and coordinating said processor and transportations in accordance with a predetermined sequence of process and transportation steps.

2. Apparatus according to claim 1 in which said processing station is a temperature-controlled reaction station having a temperature adjustor for controlling the temperature of the microtitre plate.

3. Apparatus according to claim 2 in which the temperature adjuster has a thermal cycling system for perform PCR on sample in wall bells of the microtitre plate.

4. Apparatus according to any one of the preceding claims in which a said processing station is a liquid handling station having a dispensing device with a pipetting head having a plurality of pipetting elements for dispensing liquids into respective wells of the microtitre plate.

5. Apparatus according to claim 4 in which each

pipetting elements is adapted to operate through a respective removable pipette tip.

6. Apparatus according to claim 5 in which the dispensing device comprises a release mechanism for releasing the pipette tips from their respective pipetting elements under the control of the control system.

7. Apparatus according to claim 5 or claim 6 including a pipetting tip depositary station having a plurality of position induced holders for receiving respective pipette tips released from the dispensing device under the control of the control system.

8. Apparatus according to claim 7 in which the control system includes means for recording positional and identification for a given set of release pipette tips held at the depositary station after contact with a certain liquid, and means for implementating a recycling routine whereby said predetermined sequence of processing steps involves a further step of dispensing the certain liquid, the control system causes the pipetting head to be driven, on the basis of said recorded data, to collect said given set of pipetting tips for use in the further step.

9. Apparatus according to any one of the preceding claims in which a said processing station is a viscous fluid station having means for dispensing a viscous fluid such as an oil, into wells of the microtitre plate.

10. Apparatus according to claim 9 in which the viscous

fluid station has a set of spaced, downwardly extending filaments, a viscous fluid feed for feeding the viscous fluid down the filaments and a plate-adjustment arrangement for aligning the microtitre plate with its respective wells aligned beneath respective said filaments.

11. Apparatus according to claim 10 in which the transportation mechanism is arranged to transport the plate parallel to one axis of a rectangular array of wells therein, and the spaced series of downwardly extending filaments extends parallel to the other axis of the rectangular array.

12. Apparatus according to any of the preceding claims in which the transportation mechanism includes an articulated arm with a grip at one end for gripping microtitre plate.

13. Apparatus according to claim 12 in which the articulated arm is movable bodily along an elongate track under the control of the control system.

14. Apparatus according to any one of the preceding claims in which the control system to arranged to implement processing of one microtitre plate at a said processing station while transporting another microtitre plate by the transportation system.

15. Apparatus according to any one of the preceding claims comprising error detection means for detecting an error made in the processing of microtitre plate;

means for communicating a corresponding detected

error signal to the control system; and

correction means in the control system for selecting an appropriate error correction strategy from a repertoire of such strategies stored therein and initiating implementation of the correction strategy by the apparatus.

16. Apparatus according to claim 15 in which the control system includes means for providing an error signal to an operator display in dependence on the detected error signal.

17. A method of processing chemical or biochemical samples implemented on apparatus according to any one of claims 1 to 16.

18. A method according to claim 17 wherein the processing includes carrying out Polymerase chain reaction (PCR) on multiple samples in the microtitre plate wells.

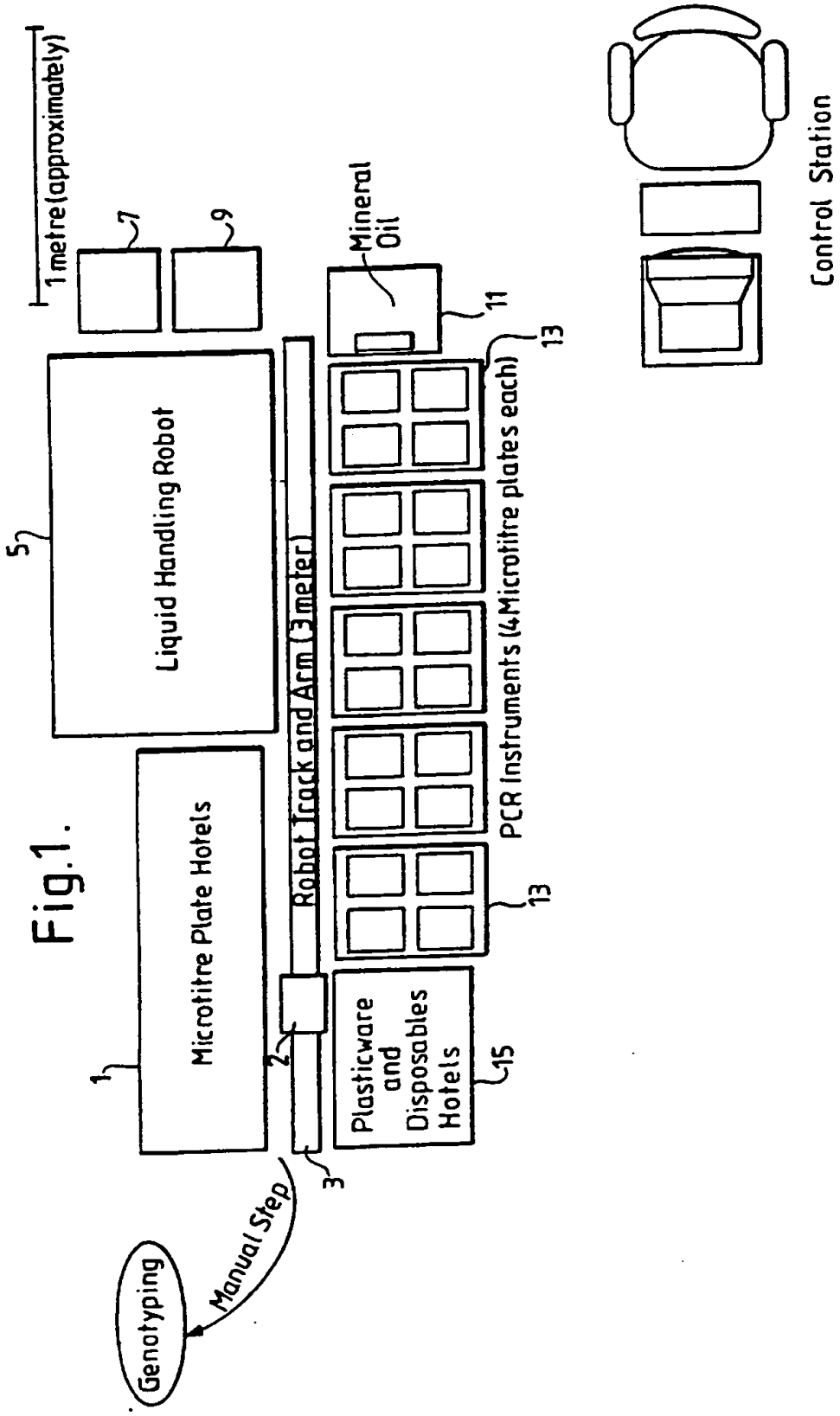
1 metre (approximately)
7
9
Mineral Oil
11
13
Control Station
Liquid Handling Robot
5
Robot Track and Arm (3 meter)
PCR Instruments (4 Microtitre plates each)
13
Microtitre Plate Hotels
1
2
Plasticware and Disposables Hotels
15
3
Manual Step
Genotyping

Fig.1.

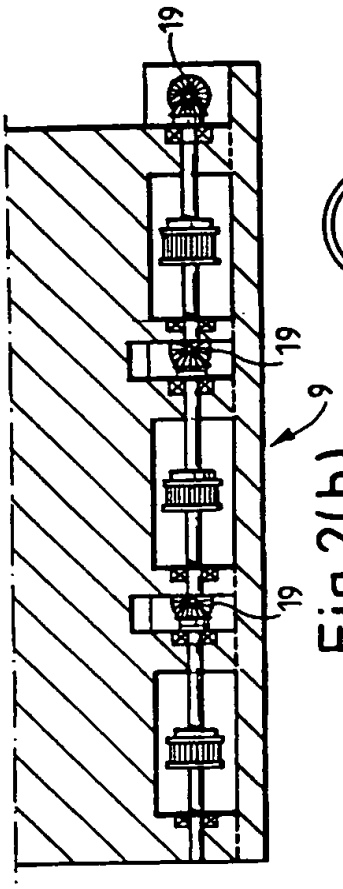

Fig.2(b)

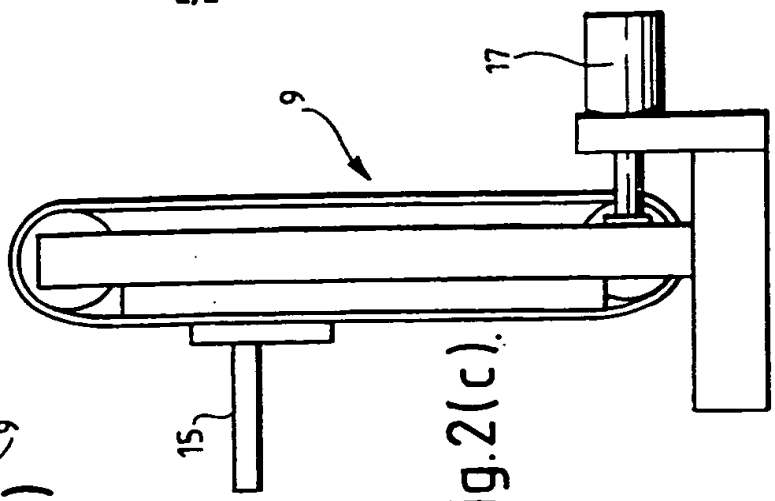

Fig.2(c).

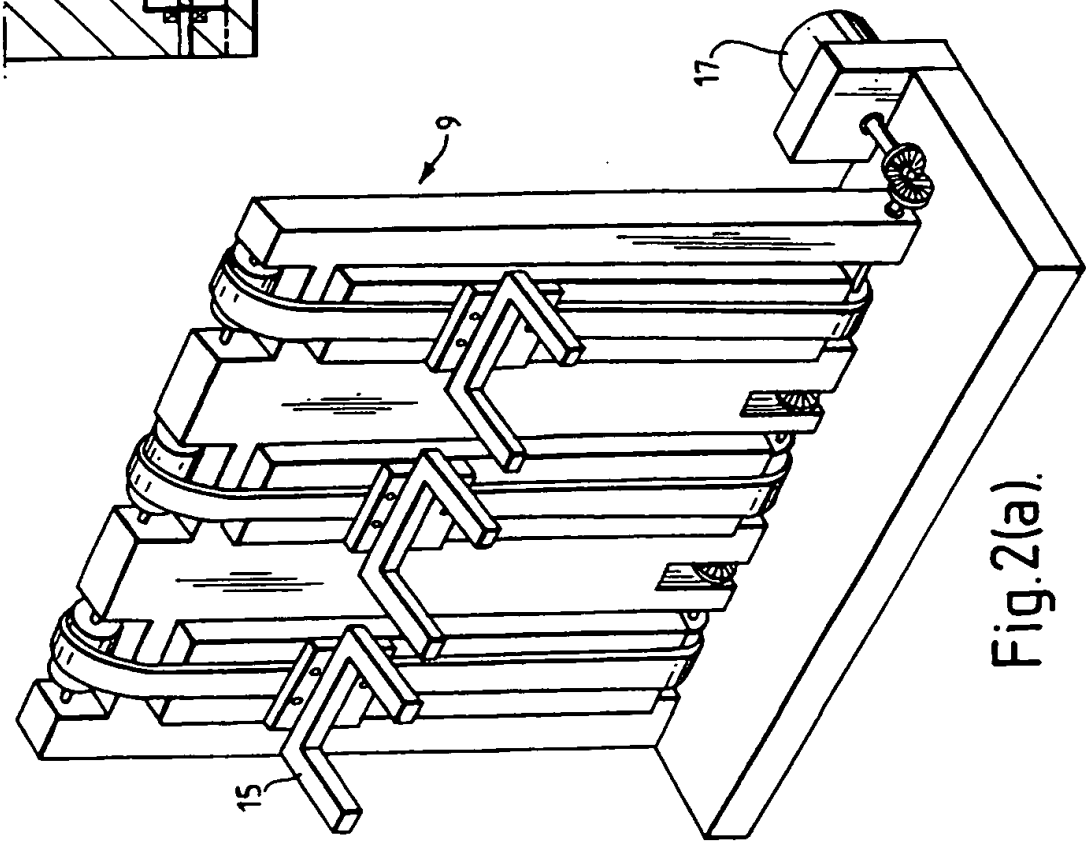

Fig.2(a).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 96/03128

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 G01N35/02 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 G01N B01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 25912 A (MEDICAL RES COUNCIL) 23 December 1993 see page 7 - page 10; figure 1 ---	1-4,17, 18
X	CHEMOMETRICS AND INTELLIGENT LABORATORY SYSTEMS, vol. 26, no. 2, 1 November 1994, pages 89-99, XP000476920 LITTLE J N ET AL: "RECENT ADVANCES IN ROBOTIC AUTOMATION OF MICROPLATE ASSAYS" see the whole document ---	1,2,4-7, 12-17
X	FR 2 633 310 A (PASTEUR INSTITUT) 29 December 1989 see page 10 - page 13; figures --- -/--	1-3,17, 18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
6 May 1997	14. 05. 97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Hodson, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 96/03128

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 91 17446 A (AUTOGEN INSTR INC) 14 November 1991 see page 7, line 30 - page 8, line 7	1,4-8
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